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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/937,150 | 03/26/2002 | Terrence R. Burke Jr. | 401371 | 6328 |

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| EXAMINER | |
|---|---|
| LUKTON, DAVID | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | |

DATE MAILED: 01/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/937,150 | BURKE JR. ET AL. | |
| | Examiner | Art Unit | |
| | David Lukton | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *39-49,67,68,73,78,85,86,91-93,107,113,116-118 and 120-139* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-49,67,68,73,78,85,116,117,120-124,126-130,133,136 and 139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are

86,91-93,107,113,118,125,131,132,134,135,137 and 138.

Pursuant to the directives of the response filed 12/3/04, claims 39, 40, 49, 116 have been amended and claims 137-139 added.

Claims 39-49, 67, 68, 73, 78, 85, 86, 91-93, 107, 113, 116-118, 120-139 remain pending. Claims 39-49, 67, 68, 73, 78, 85, 116, 117, 120-124, 126-130, 133, 136, 139 are examined in this Office action; claims 86, 91-93, 107, 113, 118, 125, 131, 132, 134, 135, 137, 138 are withdrawn from consideration.

Applicants' arguments filed 12/3/04 have been considered and found persuasive in part. The rejection of claims 39, 40, 49, 67, 78 over Larsen ('585) is withdrawn, as is the rejection of claims 39, 40, 49, 67, 78 over Horwell ('755).

✧

35 U.S.C §101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 123-124 are rejected under 35 USC. §101 because the claimed invention is not supported by a well-established utility.

Claim 123 recites that a disease can be "prevented". As it happens, there is no evidence that a disease can be "treated", but if, at some point in the future, applicants provide evidence that a disease can be successfully treated, this ground of rejection will be maintained because of the term "prevented". "Prevention" means that not a single test

subject will develop any symptoms of a disease. For example, suppose that the compound were administered to each of 1000 rats, and that a tumor were implanted into each of the rats. Suppose also, that in 999 of the rats, the tumor were completely eradicated within 10 seconds, but that one of the rats required fully six months to eradicate the tumor. Such a result would be considered "wildly successful" by any standard, yet the result would still constitute evidence of "failure" insofar as prevention is concerned. The reason is that one of the rats (out of 1000) failed to prevent the tumor from growing. The "bar" to overcome in demonstrating prevention is quite high, and not even a first step towards this goal has been undertaken. It is suggested that the term "preventing" be deleted from claim 123. (However, even if this is done, the §112, first paragraph rejection will still be maintained because of the term "treating").

There is another issue which is entirely unrelated to the foregoing. Claim 124 is drawn to a method of inhibiting MAP kinase activity in a mammal. As such, there are two categories of embodiment that are encompassed: (a) those in which the mammal has been stricken with a disease or disorder which is of a nature such that the mammal will benefit from the MAP kinase inhibition, and (b) those in which the mammal will derive no benefit from the MAP kinase inhibition, and may even suffer impairment of a needed physiological function as a result of the inhibition. This ground of rejection targets the second of these possibilities. However, this ground of rejection (in the case of claim

124, not in the case of claim 123) can be overcome merely by stating that the mammal is in need of the inhibition. The following could be used:

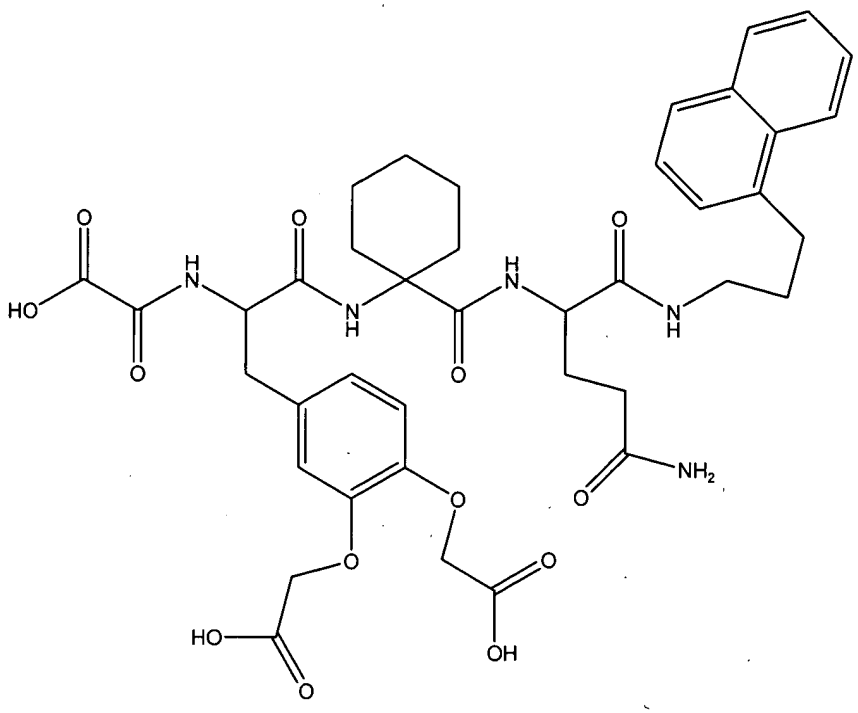
> *A method of inhibiting MAP kinase comprising administering to a mammal in need thereof a compound of claim 120.*

Claims 123-124 are also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

✧

Claims 39-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1, 10 or 11 of U.S. Patent No. 6,307,090. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed genera.

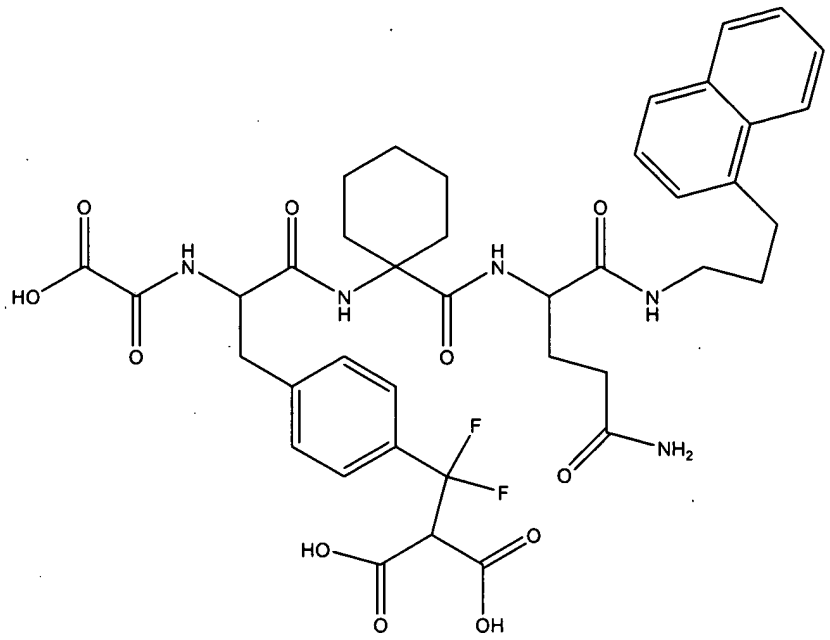
In response to this ground of rejection, applicants have amended claim 39 to exclude the possibility that "Z" can be aralkylamino when "W" is oxalyl, and at the same time, the phenyl ring (of Phe) contains any of several groups. It may be the case that this proviso is effective to exclude some of the compounds that are claimed in the patent, but there are some remaining. For example, the following compound is claimed in the patent, and encompassed by instant claim 39:



The rejection is maintained.

✧

Claim 116 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1, 10 or 11 of U.S. Patent No. 6,307,090. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed genera. Claim 11 (of the patent) is drawn to a Markush Group of eight compounds, the last of which is the following:




This compound is encompassed by instant claim 116 for the case of the phenyl group of "Y" being substituted with dicarboxy $C_1$-alkyl, wherein the alkyl group is substituted with halo. The compound of claim 11 (of the patent) is also encompassed by instant claim 116 for the case of the phenyl group of "Y" being substituted with dicarboxyhalo $C_1$-alkyl.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 123, 133 and 136 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, claim 133 is drawn to a method of treating cancer; claim 136 is drawn to a method of enhancing the therapeutic effect of an unspecified drug. In response to this characterization of claim 136, applicants have argued that the drug is specified. However, applicants are not correct on this point. The term "cancer treatment" may encompass therapeutic regimens (e.g., dietary changes or perhaps surgery) which do not require the use of a "drug"; however, to the skilled oncologist, the term "cancer treatment" is primarily directed to the use of chemotherapeutic agents. In other words, claim 136 requires (for most embodiments) two different drugs. Accordingly, the fact remains that one of those two drugs is unspecified.

In any event, neither of claims 133 or 136 is enabled. As stated on page 27, line 31, the $IC_{50}$ for MAP kinase inhibition for compound 126 is 12.5 micromolar. It is also asserted (page 28, line 10+) that compound 126 inhibits growth of MDA-MB 453 cells. Also asserted (page 28, line 12+) that compound 126 inhibits growth of MDA-MB 453/M1 breast cancer xenographs. Also asserted (page 44, line 16-17) is that compounds 11, 12 and 20a exhibited $IC_{50}$ values in the range of 100 – 500 nM using the surface plasmon resonance SH2 domain binding assay described in Yao (*J.*

*Med. Chem.* **42** 25, 1999). On page 44, line 28+, and figure 17b, it is asserted that compound 126 inhibits proliferation of MDA-MB-453 cells. Results of an experiment are also shown in figure 17a. As stated on page 3, line 23, figure 17a shows an experiment undertaken on human breast cancer cells. On page 45, line 20+, it is asserted that compound 11 inhibited production of MAP kinase in MDA-453 cells that had been treated with heregulin. On page 45, line 30+, it is asserted that compound 126 inhibited colony formation of HBC-474 and MDA-453 cell lines. However, no data is reported, and again questions of control experiments and statistical analysis come to the fore.

Thus, what applicants have shown is that one or more compounds within the claimed genus are effective to inhibit MAP kinase, to inhibit binding of an SHC phosphopeptide to a protein containing a Grb2 SH2 domain, and that one or more compounds within the claimed genus can inhibit growth of certain cells. However, no evidence is presented that there exists even one disease which can be successfully treated in a patient by administering one of the claimed compounds.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or

unpredictability of the art, and breadth of the claims. The following references discuss the matter of various attempts by oncologists to treat cancer: Viallet (*Lung Cancer* **15** (3) 367-73, 1996); Kemeny (*Seminars in Oncology* **21** (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* **9** (12) 2815-29, 2000); Giese (*Journal of Cancer Research and Clinical Oncology* **127** (4) 217-25, 2001); Garattini (*European Journal of Cancer* **37** Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* **40** (2-3) 282-308, 2001). As is evident, attempts to treat cancer using agents which have exhibited *in vitro* activity leads to "unpredictable" results.

As mentioned on page 2, line 20+ (specification) and in Yao (*J. Med. Chem.* **42** 25, 1999), proteins containing the Grb2 SH2 domain are linked to signaling events involving RAS proteins. As it happens, attempting to treat cancer using farnesyl protein transferase inhibitors leads to "unpredictable" results:

- Moasser (*Breast Cancer Research and Treatment* **73** (2) 135-44, 2002) discloses (e.g., abstract) that FT inhibitor sensitivity does not correlate with the relative expression of Ras isoforms or the inhibition of Ras processing, growth factor signaling, expression of estrogen receptor or the overexpression of growth factor receptors. Also stated (last paragraph) is that Ras is not a molecular marker to guide FT inhibition therapy. This reference does not support the proposition that attempts to treat cancer patients will necessarily result in failure. However, it does support the proposition that there may be many forms of cancer which will be resistant to the effects of FT inhibition.

- Jiang (*Molecular and Cellular Biology* **20** (1) 139-48, 2000) discloses that while AKT2- transformed NIH 3T3 cells are sensitive to FTI-277, but that *ras*-transformed NIH 3T3 cells are not. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.

- Prendergast (*Molecular and Cellular Biology* **14** (6) 4193-202, 1994) discloses that

the FT inhibitor L-739,749 inhibited growth of ras-transformed fibroblasts. However, L-739,749 had no effect on the growth, morphology, or actin organization of v-*raf*-transformed cells. This supports the proposition that one cannot predict which cells will be sensitive to FT inhibitors.

- Njoroge (*J. Med. Chem.* 40 (26) 4290-301, 1997) discloses that the Ras farnesyl-protein transferase inhibitor SCH 44342 did not show appreciable *in vivo* antitumor activity. This supports the proposition that *in vitro* activity is not necessarily predictive of therapeutic efficacy.

- Lerner (*Oncogene* **15** (11) 1283-8, 1997) discloses that the Ftase inhibitor FTI-277 is highly effective at blocking oncogenic H-Ras but not K-Ras4B processing and signaling. The results obtained demonstrate that while FTI-277 inhibits N-Ras and H-Ras processing in the human tumor cell lines evaluated, inhibition of K-Ras processing requires both an FTase inhibitor and a GGTase I inhibitor.

- Whyte (*J Biol Chem* **272**, 14459, 1997) discloses that geranylgeranyl transferase-1 is structurally related to farnesyl transferase, and that geranylgeranyl transferase-1 may alternatively prenyl K-Ras, thereby bypassing the effect of FPTase inhibition.

- Sharma (*Annals of Oncology* **13** (7) 1067-71, 2002) discloses results of a phase II trial of SCH 66336, an FPTase inhibitor, in patients with metastatic colorectal cancer. No objective responses were observed. It is concluded that future development of this compound cannot be recommended as monotherapy in this disease.

Thus, attempts to treat cancer lead, in general, to "unpredictable" results, as do attempts to treat cancer using Ftase inhibitors. Accordingly, it stands to reason that in attempting to treat cancer in humans using compounds which inhibit binding of an SHC phosphopeptide to a protein containing a Grb2 SH2 domain, "unpredictable" results will be obtained.

Accordingly, "undue experimentation" would be required to practice the invention of claims 133 and 136.

In response to the foregoing, applicants have pointed to Bardelli (*Oncogene* **18**, 1139-1146, 1999). Applicants have argued that this reference supports the proposition that compounds which inhibit Grb2 binding (to an entity which applicants have not identified) can treat any and all forms of cancer. However, applicants are not correct. Bardelli undertook experiments in which fibroblasts that were transformed by *Tpr-Met* signalling mutants were injected into mice, with the result that metastatic colonization occurred in the lungs. In a related vein, cells transformed by either *Tpr-Met*$^{2xBrb2}$ or Tpr-Met$^{2xPI3K}$ were impared in their metastatic potential. Bardelli also argues that concomitant activation of Grb2 and PI 3-kinase is required for *Tpr-Met*- mediated metastasis. However, Bardelli did not show that there exists even one form of cancer that can be successfully treated with a compound that inhibits the binding of Grb2 to anything. Bardelli did not even show that there exists one type of tumor cell for which growth is inhibited *in vitro* (or *in vivo*) by an inhibitor of Grb2 binding. Applicants characterization of the reference, and the conclusions that can be drawn therefrom is entirely incorrect. But suppose, at some point in the future, that applicants are able to find a reference that shows that when a specific inhibitor of Grb2 binding is administered to tumor-bearing rats, the mass of the tumor is reduced. Even this would not support claims drawn to treatment of cancer. The first issue would be whether the claimed compounds are as effective in inhibiting Grb2 binding as the compound in the reference. If the claimed compounds are not as effective *in vitro*, they are unlikely to

be as effective *in vivo*. And even if the claimed compounds are as effective *in vitro*, as the compounds in the reference (the reference being one which has not been identified by applicants, and probably never will be), it would not follow therefrom that the claimed compounds will be as effective *in vivo*. Issues such as pharmacokinetics and biodistribution would have to be assessed.

Next, suppose that applicants actually undertook experiments on rats and showed that for a specific type of cancer, the claimed compounds are actually effective at treating that form of cancer. Suppose, for the sake of argument, applicants could demonstrate efficacy in the case of breast cancer. Even if that were shown to be the case, it would not follow that the growth and metastasis of any and all forms of cancer can be slowed to an extend to achieve therapeutic efficacy. The term "cancer" or "tumor" encompasses a wide variety of proliferative diseases, such as the following: prostate cancer, lung cancer, colon cancer, rectal cancer, bladder cancer, Non-Hodgkin Lymphoma, melanomas of the skin, cancer of the kidney and renal pelvis, pancreatic cancer, oral cancer, esophagal cancer, ovarian cancer, thyroid cancer, stomach cancer, brain cancer, multiple myeloma, liver and intrahepatic bile duct cancer, acute myeloid leukemia, chronic lymphocytic leukemia, Hodgkin's Lymphoma, testicular cancer, intestinal cancer, chronic myeloid leukemia, acute lymphocytic leukemia, cancer of the vulva, gallbladder cancer, malignant mesothelioma, bone cancer, joint cancer, cancer of the hypopharynx, cancer of the eye, cancer of the nose, cancer of the ureter, cancer of the peritoneum,

gastrointestinal carcinoid tumors, bladder cancer, melanoma, breast cancer, non-hodgkin's lymphoma, ovarian cancer, endometrial cancer, pancreatic cancer, kidney cancer (renal cell), prostate cancer, leukemia, non-melanoma cancer of the skin. Also included are sarcomas and carcinomas, such as the following: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, lymphoma, multiple myeloma, Waldenströom's macroglobulinemia, and heavy chain disease. There is no evidence of record that there exists any one agent that is effective against all of these cancer types, or most of them. The skilled oncologist would not regard it as realistic

that one can extrapolate from a showing of inhibition of growth of one cancer cell type to inhibition of growth of all cancer cell types.

It remains the case that "undue experimentation" would be required to practice the invention of claims 123, 133 or 136.

✧

Claims 39-49, 67, 68, 73, 78, 85, 116, 117, 120-124, 126-130, 133, 136, 139 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 39, it is recited, in reference to "Y", that the alkyl portion of the substituents can be substituted with "keto". However, a "keto" group must bonded to two groups, not one. Accordingly, the claim is rendered indefinite as to what other substituent can be bonded to the keto group.

- In claim 39, the following phrase is present (at two locations):

  "wherein... the substituents may be ... substituted"

  However, the phrase "the substituents" lacks antecedent basis.

- In claim 40, it is recited, in reference to "Y", that the alkyl portion of the substituents can be substituted with "keto". However, a "keto" group must bonded to two groups, not one. Accordingly, the claim is rendered indefinite as to what other substituent can be bonded to the keto group.

- Claim 41 permits substitutent variable $R_3$ to be a group other than hydrogen. However, claim 40, upon which claim 41 depends, does not permit $R_3$ to be a group other than hydrogen. For example, if $R_3$ is methyl and $R_5$ and $R_6$ are both hydrogen, the result is not a carboxymethyl group; rather, the resulting substituent is

an ester of a carboxymethyl group. Claim 40 does not permit the phenyl group of "Y" to be substituted with an ester of a carboxyalkyl group. Accordingly, the claim dependence is not proper. Perhaps one option would be to cast claim 41 in independent form.

- Claim 41 permits substitutent variable "E" to be a group other than hydrogen. However, claim 40, upon which claim 41 depends, does not permit variable "E" to be a group other than hydrogen. Accordingly, the claim dependence is not proper. Perhaps one option would be to cast claim 41 in independent form.

- Claim 73 requires that "Z" contain a heterocycle. At the same time, however, this claim permits variables "F" and "G" to both represent a carbon atom. For the case of "F" and "G" simultaneously representing a carbon atom, the claim is inherently contradictory.

- Claim 73 recites that "$Q_2$" can be a substituent other than hydrogen. However, claim 39, upon which claim 73 depends, makes reference only to an aryl heterocyclic group, not a "substituted" aryl heterocyclic group. Accordingly, the claim dependence is not proper.

- In claim 116, it is recited, in reference to "Y", that the alkyl portion of the substituents can be substituted with "keto". However, a "keto" group must bonded to two groups, not one. Accordingly, the claim is rendered indefinite as to what other substituent can be bonded to the keto group.

- Claim 120 is recited to be dependent on claim 39. However, a subgenus containing the compound of claim 120 has now been excluded from claim 39. Accordingly, the claim dependence is not proper.

- Claim 123 contains the following phrase:

  "comprising administering inhibiting proliferation"

  The presence of this phrase gives rise to a grammatical error.

- Claim 123 recites that a "state" can be "preventing". If a physiologist were so inclined, how would he go about preventing a state?

✧

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 39, 40, 49, 72, 78, 85 are rejected under 35 U.S.C. §102(a) as being anticipated by Al-Obeidi (USP 5,849,510).

As indicated previously, Al-Obeidi discloses (col 22, line 15+) the following compound:

Ac-Tyr-Ile-Arg-NH-$CH_2$-pyridyl

This anticipates claim 39 when the substituent variables are as follows:

Y is Phe substituted with hydroxyl
W is alkylcarbonyl
n is 2
Z is arylalkylamino wherein the "aryl" group is pyridine.

In response, applicants have amended the claim in an attempt to overcome this ground of rejection. However, the claims can be rejected in accordance with another interpretation.

The fact is that pyridine is every bit as aromatic as benzene or naphthalene. The term "aryl", in the absence of further qualification, encompasses any compound that is aromatic, regardless of whether it might contain a nitrogen atom or not. The argument could stop here and be sufficient. But in addition, it appears that, at the time the specification was written, applicants were in agreement with the examiner on this point. For example, at page 10, lines 3-4, and page 10, lines 32-33, the following is recited (paraphrased slightly):

"the heteroaryl portion of arylalkyl can be substituted or unsubstituted".

Thus, applicants recognize that aromatic compounds do not lose their aromaticity merely because an $sp^2$-hybribidized carbon atom has been replaced with a nitrogen atom. Perhaps one option here would be to recite the term *carbocyclic aryl*, rather than just "aryl". Or else a proviso could be added which states that the term "aryl" does not include heteroaryl.

The rejection is maintained.

✧

Claims 39-40 and 116 are rejected under 35 U.S.C. §102(e) as being anticipated by Burke (USP 6,307,090).

Some of the compounds disclosed by Burke have been indicated previously. In response, applicants have amended the claims, and have argued that the amendment overcomes the rejection. The first point is that, even if there were a statute or court opinion which stated that only the subject matter that is recited in claims can form the basis

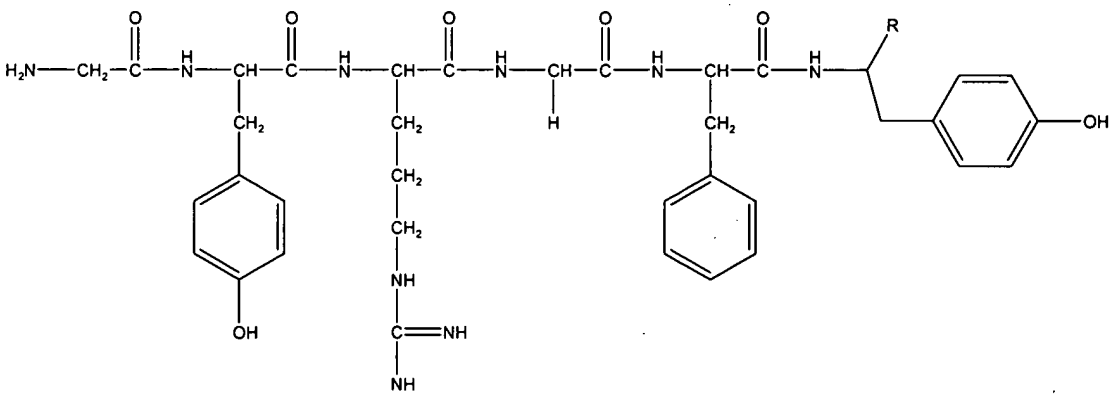
for a §102 rejection (and there is obviously no such statute or court opinion), this ground of rejection could be maintained, for the reasons given above in the double patenting rejection. But in addition, one may look to compounds in any part of the disclosure. For example, in scheme 3 of the patent (column 29), various compounds are disclosed that are encompassed by the instant claims. If applicants are going to attempt to overcome this ground of rejection by amendment, it is suggested that each and every compound that is disclosed in the patent be excluded.

The rejection is maintained.

✧

Claims 39-40 are rejected under 35 U.S.C. §102(e) as being anticipated by Hiyoshi (USP 5,824,862).

Hiyoshi discloses (col 53) SEQ ID NO: 13, which is the following (R = carboxyl):



This peptide anticipates the claims when applicants' substituent variables correspond as follows:

W = methylcarbonyl which is substituted with amino

Y = phenylalanine which is substituted with hydroxyl

$AA^1$ = arginine

$AA^2$ = glycine

$AA^3$ = phenylalanine

n = 3

Z = phenethylamino which is substituted with carboxyl and with hydroxyl.

In response, applicants have argued that the language of claim 39 is such as to exclude any substitutions on alkyl groups. However, in at least two locations in claim 39, the following phrase is present:

"wherein the ...alkyl portions of the substituents may be ... substituted with... carboxyl"

Thus, it is not made clear which alkyl groups can be further substituted. On this basis alone, the rejection is justified. But in addition to this, there is another rationale. As discussed in the §102(e) over Lunney ('697), it is apparent from a comparison of claims 40 and 41 that any hydrogen atom can be removed and replaced with another group not specified in the claims. According to this line of reasoning, a hydrogen atom of the C-terminal phenethyl group could be removed and replaced with carboxyl.

As a first step in the direction of overcoming this ground of rejection, it is suggested that applicants amend claims 39 and 40 to make it clear which alkyl groups can be substituted, and which cannot.

The rejection is maintained.

✧

Claims 39-40 are rejected under 35 U.S.C. §102(e) as being anticipated by Harding (USP 6,022,696)

Harding discloses (col 59) SEQ ID No: 1, and (col 69) SEQ ID No: 14. These are, respectively, the following:

VYIHPF

KYIHPF

The first of these is encompassed by claim 39 when the substituent variables correspond as follows:

W = alkylcarbonyl which is substituted with amino
Y = phenylalanine which is substituted with hydroxyl
$AA^1$ = Ile
$AA^2$ = His
$AA^3$ = Pro
n = 3
Z = phenethylamino which is substituted with carboxyl

In response to this ground of rejection, applicants have argued that the term "alkylamino" is intended to mean unsubstituted alkylamino. However, the claims are silent on this

matter. And as discussed in the §102(e) over Hiyoshi ('862), there are two rationales for believing that the term "alkylamino" encompasses substitituted alkylamino.

The rejection is maintained.

✧

Claims 39-40 are rejected under 35 U.S.C. §102(e) as being anticipated by Landry (USP 5,948,658).

Landry discloses (col 67) SEQ ID NO: 76 which has the following sequence:

D-Y-N-M-Y

This peptide anticipates the claims when applicants' substituent variables correspond as follows:

W = 2-methylpropionyl which is substituted with amino and with carboxyl

Y = phenylalanine which is substituted with hydroxyl

$AA^1$ = Asn

$AA^2$ = Met

n = 2

Z = phenethylamino which is substituted with carboxyl and with hydroxyl.

In response to this ground of rejection, applicants have argued that the term "alkylamino" is intended to mean unsubstituted alkylamino. However, the claims are silent on this matter. And as discussed in the §102(e) over Hiyoshi ('862), there are two rationales for believing that the term "alkylamino" encompasses substitituted alkylamino.

The rejection is maintained.

✧

Claims 39-40 are rejected under 35 U.S.C. §102(e) as being anticipated by Dimaio (WO 98/50421)

Dimaio discloses a compound on page 35 (line 11+) which is encompassed by the instant claims.

Thus, the claims are anticipated.

✧

Claims 39-40 are rejected under 35 U.S.C. §102(e) as being anticipated by Lunney (USP 5,922,697).

Lunney discloses a compound at col 28, lines 27-45 (as dicussed further below).

The issue here is one of claim interpretation. Neither of claims 39-40 recites that the hydroxyl group of tyrosine can be phosphorylated. However, that is not the end of the analysis. As indicated above in the §112, second paragraph rejection, upon comparing claim 41 with claim 40, one finds that, according to applicants, the claimed compounds are not limited to those explicitly recited. That is, according to applicants, the structures provided are merely a starting point for structural modifications. According to applicants, one can start with a structure provided in the claims, and replace a hydrogen atom with another group that is not suggested by either of claims 39 or 40. According to applicants' own reasoning then, the hydrogen atom of the hydroxyl group (present on

tyrosine) can be removed and replaced with another group. As such, claim 40 does not exclude compounds in which that other group is phosphate.

Thus, according to one interpretation of the claims, they are anticipated.

✧

The following is a quotation of 35 USC. §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 39-40 are rejected under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103 as obvious over Lunney (USP 5,922,697).

Lunney discloses a compound at col 28, lines 27-45. This particular compound might not be encompassed by the instant claims, but the immediate precursor to this compound **is**. As stated (col 28, line 47), the compound was prepared analogously to

the compound of example 1. The synthesis of example 1 (col 16, line 30+) was carried out by first coupling two fragments as follows:

H-Glu(OtBu)-NMe-cyclohexylpropyl + Ac-Tyr →

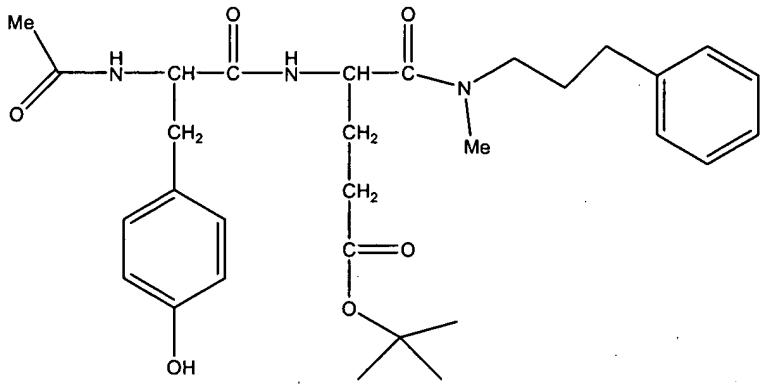
Ac-Tyr-Glu(OtBu)-NMe-cyclohexylpropyl

Subsequently, the hydroxyl group on tyrosine was phosphorylated. The phosphorylation reaction, however, is not relevant to this gound of rejection. What matters is the structure of the compound that was subject to the phosphorylation reaction. Consider again the compound that is the immediate precursor to the compound of example 19 (structure col 28, line 31+). According to the teaching of Lunney, the target compound was prepared by first coupling two fragments as follows:

H-Glu(OtBu)-NMe-phenylpropyl + Ac-Tyr →

Ac-Tyr-Glu(OtBu)-NMe- phenylpropyl

Thus, Lunney provides a disclosure of the following compound:



[The tyrosine is subsequently phosphorylated, but that is not relevant to the basis of this rejection]. This intermediate compound (which is subject to phosphorylation) is encompassed by the cited claims.

The claims are anticipated, since the reference can be said to disclose at least one compound which falls within the scope of the cited claims. Alternatively, one could argue that the claims are merely obvious, since one has to go back to the synthesis of example 1 to recognize that the reference provides an affirmative teaching of the compound in question.

*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.